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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/663,538	LU ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7,13,14 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-12 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: Appendices A,B

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 16 January 2004 has been entered in full.

Election/Restrictions

Applicant's election without traverse of Group A, claims 1-6, 8-12, and 15-17, drawn to an isolated CLASP-2 polynucleotide, an expression vector, a host cell system, and a method of producing a CLASP-2 polypeptide in the reply filed on 20 November 2006 is acknowledged. Applicant's election without traverse of DLG1 as the species of protein containing a PDZ domain in the reply filed on 20 November 2006 is acknowledged.

Applicant's election with traverse of the nucleic acid sequence of SEQ ID NO: 1 and the amino acid sequence of SEQ ID NO: 2 in the reply filed on 20 November 2006 is acknowledged. The traversal is on the ground(s) that SEQ ID NOs: 1, 3, 5, 9 are splice variants of the same gene. Applicant also argues that MPEP § 2435 provides that in most cases up to ten sequences will be examined. This is not found persuasive because each nucleotide sequence comprising Groups 1-4 and each amino acid sequence comprising Groups 5-8 is a unique sequence requiring a unique search of the prior art. Each polynucleotide listed in Groups 1-4 is a different length and is composed of different nucleic acids, suggesting that each encodes a different polypeptide. Further, each polypeptide listed in Groups 5-8 is a different length and is composed of different amino acids, suggesting that each is a different polypeptide with diverse functional and structural features. Also, with the ever-increasing size of the nucleic acid databases, it is no longer reasonable to search 10 nucleotide sequences in a single application. Searching all of the

sequences in a single patent application would provide an undue search burden on the Examiner and the USPTO's resources because of the non-coextensive nature of these searches.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7, 13-14, and 18-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 20 November 2006.

Claims 1-6, 8-12, and 15-17 are under consideration in the instant application as they read upon the elected polynucleotide sequence of SEQ ID NO: 1 (which encodes the amino acid sequence of SEQ ID NO: 2).

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 16 January 2004 has been considered by the examiner. It is noted that several pages of the IDS submitted by Applicant are PTO-892 forms submitted in parent cases. Currently, these pages have been crossed off by the Examiner because several of the references have been cited in duplicate, as well as for clarity of the record. MPEP § 609.02(A)(2) states that "[I]f resubmitting a listing of the information, applicant should submit a new listing that complies with the format requirements in 37 CFR 1.98(a)(1). Applicants are strongly discouraged from submitting a list that includes copies of PTO/SB/08 ** or PTO-892 forms from other applications. A completed PTO/SB/08 ** form from another application may already have initials of an examiner and the application number of another application. This information will likely confuse the record."

Sequence Compliance

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). **Specifically, the specification discloses sequences at pages 7, 40, 41, 114, and 121 that are not accompanied by the required reference to the relevant sequence identifiers.** This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Specification

2. The disclosure is objected to because of the following informalities:

2a. Patent applications are referenced throughout the disclosure (pg 2, line 30; pg 37, line 21; pg 126, lines 16-21). The status of the applications must be updated.

2b. At page 119, line 5, it is not clear of the meaning of the following sentence: "(Please provide some specific regions)."

2c. The specification at page 120, line 7 contains a reference to a specific product catalog number, which is subject to change over time. (Note, this issue could be overcome by adding the complete catalog information, such as year and volume or by deleting the catalog number.)

2d. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See page 16, lines 19). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

2e. The specification refers to Figures which were deleted in the amendment of 16 January 2004. Please see, for example, pages 25, 45, 47, 68, 113, 114, 115, 125.

2f. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "NUCLEIC ACID MOLECULE ENCODING A CLASP-2 TRANSMEMBRANE PROTEIN".

Appropriate correction is required.

Claim Objections

3. Claims 1-4, 6, 15 are objected to because of the following informalities:

3a. Claim 1, 4-6, 15 recite non-elected groups.

3b. Claim 1(c) at line 2 is missing the term "least" before the phrase "25 contiguous residues".

3c. Claim 4, line 1 requires the insertion of a space keystroke between the word "claim 1" and "that".

3d. Claims 1-3, 6, and 15 use the acronyms "CLASP-2", "PDZ", "PSD95", "DLG1", and "neDLG" without first defining what they represent in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and § 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6, 8-12, and 15-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

Specifically, claims 1-6, 8-12, and 15-17 are directed to an isolated Cadherin-like asymmetry protein-2 (CLASP-2) polynucleotide wherein the polynucleotide is (a) a polynucleotide that has the sequence of SEQ ID NO: 1, (b) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide having the sequence of SEQ ID NO: 2 or an allelic variant or homologue, (c) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2, or (d) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1. The claims further recite that the polynucleotide encodes a polypeptide having the sequence of SEQ ID NO: 2 that specifically binds to a PDZ domain of DLG1. The claims recite an isolated CLASP-2 polynucleotide comprising a nucleotide sequence that has at least 90% identity to SEQ ID NO: 1. The claims also recite an expression vector comprising the polynucleotide, a host cell, and a method for producing the polypeptide.

The specification asserts that the CLASP-2 polynucleotide (SEQ ID NO:1) and polypeptide (SEQ ID NO: 2) of the present invention are involved in a variety of cellular processes, particularly related to immune function, T cell activation, regulation of T cell and B

cell interactions, and in the organization, establishment, and maintenance of the "immunological synapse" (including signal transduction, cytoskeletal interactions, and membrane organization) (pg 22, lines 1-7; pg 21, lines 1-5). However, the instant specification does not teach any significant characteristics of the CLASP-2 polynucleotide (SEQ ID NO: 1) or polypeptide (SEQ ID NO: 2). The specification also does not disclose any methods or working examples that indicate the polynucleotide and polypeptide of the instant invention are involved in any of the abovementioned activities. Since significant further research would be required of the skilled artisan to determine how the claimed polypeptide is involved with the above-mentioned activities, the asserted utilities are not substantial. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the following as patentable utilities for the claimed putative polynucleotide (SEQ ID NO: 1):

1) to detect the expression of CLASP-2 in cells (pg 47, lines 28-29; pg 53-56)

2) in the diagnosis of a disorder or disease resulting from aberrant expression of CLASP-2 (pg 48-49)

3) as hybridization probes for cDNA and genomic DNA (pg 48, lines 16-31; pg 49)

4) as primers for a nucleic acid amplification (pg 48, lines 16-31; pg 49)

5) to treat, detect, or modulate immune system disorders, hematopoietic cell disorders, allergic reactions, organ rejection or graft-versus-host disease, inflammation, infectious agents (pg 50, lines 21-34 through the top of pg 53)

6) to engineer hammerhead motif ribozyme molecules (pg 60, lines 21-33; pg 61, lines 29-33)

7) for gene therapy (pg 62-65)

8) to construct a transgenic animal (pg 66-67)

9) in chromosome mapping (pg 68, lines 1-23)

10) to screen CLASP-2 agonists and antagonists (pg 47, lines 25-26)

Each of these shall be addressed in turn.

1) to detect the expression of CLASP-2 in cells. This asserted utility is not specific or substantial. The specification does not disclose a specific target sequence. The specification does not disclose the cell types that express CLASP-2. Significant further experimentation would be required of the skilled artisan to identify cells and/or tissues and organs with CLASP-2. Since this asserted utility is also not present in mature form so that it could be readily used in real world sense, the asserted utility is not substantial.

2) in the diagnosis of a disorder or disease resulting from aberrant expression of CLASP-2. This asserted utility is not specific or substantial. The specification does not disclose disorders associated with a mutated, deleted, or translocated CLASP-2 gene. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form so that it could be readily used in real world sense, the asserted utility is not substantial.

3) as hybridization probes for cDNA and genomic DNA. This asserted utility is not substantial or specific. Hybridization probes can be designed from any polynucleotide sequence. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) as primers for a nucleic acid amplification. This asserted utility is not substantial or specific. Primers can be designed from any polynucleotide sequence. Further, the specification

does not disclose a specific DNA target. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

5) to treat, detect, or modulate immune system disorders, hematopoietic cell disorders, allergic reactions, organ rejection or graft-versus-host disease, inflammation, infectious agents. This asserted utility is not specific or substantial. The specification does not disclose disorders associated with a mutated, deleted, or translocated CLASP-2 gene (SEQ ID NO: 1). The specification does not disclose which disorders are associated with altered levels of the CLASP-2 gene. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

6) to engineer hammerhead motif ribozyme molecules. This asserted utility is not specific or substantial. Ribozymes can be designed from any DNA/RNA sequence. Additionally, the specification does not disclose a specific DNA/RNA target. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

7) for gene therapy. This asserted utility is not specific or substantial. The specification does not disclose diseases associated with a mutated, deleted, or translocated CLASP-2 gene of SEQ ID NO: 1. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

8) to construct a transgenic animal. This asserted utility is not specific or substantial. The specification does not disclose diseases associated with a mutated, deleted, or translocated

CLASP-2 gene (SEQ ID NO: 1). Significant further experimentation would be required of the skilled artisan to identify such a disease. The specification discloses nothing about whether the gene will be "knocked in" or "knocked out" or what specific tissues and cells are being targeted. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

9) in chromosome mapping. This asserted utility is not specific or substantial. Such assays can be performed with any polynucleotide. Further, the specification does not disclose a specific DNA target. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

10) to screen CLASP-2 agonists and antagonists. This asserted utility is not specific or substantial. Such assays can be performed with any polynucleotide. Nothing is disclosed about how the polynucleotide is affected by the compounds. Additionally, the specification discloses nothing specific or substantial for the CLASP-2 agonists and antagonists screened in this method. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Additionally, the specification of the instant application also teaches that the CLASP-2 C-terminal 20 amino acids bind to PDZ domain-containing proteins (pg 10, lines 8-31 pg 30-31; 122-123; Figure 9). However, relevant literature teaches that PDZ domains are among the commonest protein domains represented in sequence genomes and analysis of the human genome estimates the presence of 440 PDZ domains in at least 259 different proteins (Hung et al. J Biol Chem 277(8): 5699-5702, 2002; ¶ 1). Therefore, the asserted utility of CLASP-2 or

CLASP-2 related compounds to bind to PDZ-domain containing proteins and to mediate changes in multiple protein-protein interactions involved in the function of lymphoid tissues is not specific or substantial (specification, pg 30, lines 27-32). At least 258 other PDZ-domain containing proteins could bind to CLASP-2 and/or the PDZ-domain containing proteins used in the experiments of the instant application. The specification also does not disclose any *specific* proteins that CLASP-2 may interact with in lymphoid tissue or during cell signaling. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Furthermore, the utilization of CLASP-2 expression to determine T-cell activation is not a specific and substantial utility. Although Applicant indicates that CLASP-2 expression levels decrease at 1 hour, 2 hours, and 4 hours after activation (pg 125, lines 4-14), it cannot be determined if this decrease is a significant difference as compared to T-cells that have not been activated. If the decrease in CLASP-2 expression is not significant between the two cell types, then this utility is not specific because the skilled artisan would not be able to distinguish activated T-cells from inactivated T-cells. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial. Applicant is encouraged to submit any evidence under 37 C.F.R. 1.132 that would indicate a significant difference between the expression of CLASP-2 in activated and inactivated T-cells.

5. Claims 1-6, 8-12, and 15-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 1-3, 6, 8-12, and 15-17 would remain rejected under 35 U.S.C. § 112, first paragraph. The specification discloses that "the CLASP-2 variants of the invention can contain alterations in the coding regions, non-coding regions, or both" (pg 44, lines 10-11). The specification teaches that known methods of protein engineering and recombinant DNA technology can generate variants to improve or alter the characteristics of the CLASP-2 polypeptides (pg 46, lines 3-34). However, the specification does not teach any allelic variants or homologs of the CLASP-2 polynucleotide or polypeptide. The specification does not disclose (i) a polynucleotide that encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2 or (ii) a polynucleotide that has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1. The specification also does not teach a nucleic acid sequence with 90% sequence identity to the nucleotide sequence of SEQ ID NO: 1. Furthermore, the specification does not disclose any chromosomal locus for CLASP-2, which is a necessity since an allelic variant must be at the same locus. Undue experimentation is required to identify the locus and map variants to determine which ones are alleles. Additionally, the specification does not teach functional or structural characteristics of any polynucleotide variants in the context of a cell or organism. Claim 15 also recites the phrase "...a CLASP-2 protein as shown in SEQ ID NO: 2" [emphasis added] and thus, is broadly interpreted by the Examiner as reading upon DNA molecules that encode any CLASP-2 protein fragment of SEQ ID NO: 2, including sequences only 6 nucleic

acids in length. However, the specification does not teach any variant, fragment, or derivative of the CLASP-2 protein and polynucleotide other than the full-length amino acid sequence of SEQ ID NO: 2 and the full-length nucleic acid sequence of SEQ ID NO: 1. The specification also does not teach functional or structural characteristics of the polynucleotide and polypeptide variants, fragments, and derivatives encompassed by the claims.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional

configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Additionally, the Examiner has interpreted claims 10-12 as reading on isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that CLASP-2 gene can be expressed in transgenic animals and any technique known in the art may be used to introduce a CLASP-2 transgene into animals to produce the founder lines of transgenic animals (pg 66-67). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated CLASP-2 gene of SEQ ID NO: 1 is demonstrated to express the CLASP-2 peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has CLASP-2 "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to

factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Additionally, for example, the specification discloses that two possible techniques used to introduce a CLASP-2 transgene into animals include pronuclear microinjection and gene targeting in embryonic stem cells (pg 66, lines 28-31). However, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even rarer than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention. Furthermore, regarding gene targeting in embryonic stem cells, the specification does not provide guidance for identifying and isolating embryonic stem cells or for identifying other embryonal cells which are capable of contributing to the germline of any animal. At the time of filing, Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species...However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (Campbell et al. Theriology 47(1): 63-72, 1997; see pg 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than

mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

The specification also discloses that nucleic acids encoding the CLASP-2 polypeptide can be used for gene therapy (pg 62-65). However, the specification does not teach any methods or working examples that indicate a CLASP-2 nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the CLASP-2 nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express a CLASP2 nucleic acid into the cell of an organism.

Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a CLASP-2 nucleic acid in the cell of an organism or be able to produce a CLASP-2 protein in that cell. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated host cell...").

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen the same for activity, and to generate a transgenic animal expressing the CLASP-2 protein and to introduce and express a CLASP-2 nucleic acid in a cell of an organism for therapy; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity and how to introduce a CLASP-2 nucleic acid in the cell of an organism to be able produce that CLASP-2; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the unpredictability of making transgenic animals and of transferring genes into an organism's cells; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 1-6, 8-12, and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6, 8-12, and 15-17 are directed to an isolated Cadherin-like asymmetry protein-2 (CLASP-2) polynucleotide wherein the polynucleotide is (a) a polynucleotide that has the sequence of SEQ ID NO: 1, (b) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide having the sequence of SEQ ID NO: 2 or an allelic variant or homologue, (c) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2, or (d) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1. The claims further recite that the polynucleotide encodes a polypeptide having the sequence of SEQ ID NO: 2 that specifically binds to a PDZ domain of DLG1. The claims recite an isolated CLASP-2 polynucleotide comprising a nucleotide sequence that has at least 90% identity to SEQ ID NO: 1. The claims also recite an expression vector comprising the polynucleotide, a host cell, and a method for producing the polypeptide. The claims do not require that the polynucleotide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polynucleotides that are defined only by sequence identity.

The specification discloses that "the CLASP-2 variants of the invention can contain alterations in the coding regions, non-coding regions, or both" (pg 44, lines 10-11). The specification teaches that known methods of protein engineering and recombinant DNA technology can generate variants to improve or alter the characteristics of the CLASP-2 polypeptides (pg 46, lines 3-34). To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing

identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity or a certain number of contiguous bases. The Examiner has also broadly interpreted claim 15 as reading upon DNA molecules that encode any CLASP-2 protein fragment of SEQ ID NO: 2, including sequences only 6 nucleic acids in length ("...a CLASP-2 protein as shown in SEQ ID NO: 2" [emphasis added]). There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polynucleotide species (SEQ ID NO: 1) and one polypeptide species (SEQ ID NO: 2) is not adequate written description of an entire genus of functionally equivalent polynucleotides which incorporate all variants and fragments and variants with at least 90% sequence identity to the nucleic acid sequence of SEQ ID NO: 1.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated CLASP-2 polynucleotide that has the sequence of SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

8. Claim 5 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The invention appears to employ novel nucleic acid molecules (i.e., clones AVC-PD1, AVC-PD2, etc.). Since the nucleic acid molecules are essential to the claimed

invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the nucleic acid molecules are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules. The specification does not disclose a repeatable process to obtain the nucleic acid molecules and it is not apparent if the nucleic acid molecules are readily available to the public. It is noted that Applicant has deposited the nucleic acid molecules (pg 110, lines 31-34; pg 111, lines 1-9 of the specification), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the nucleic acid molecules will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include such, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-6, 8-12, and 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions of **A** X SSC and **B** % SDS at **C**°C"), claims 1-6, 8-12, and 15-17 fail to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1 and 15-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Pianese et al. (Genbank Accession No. X68101; 24 February 1999). It is noted that the Examiner has broadly interpreted claim 15 as reading upon DNA molecules that encode any CLASP-2 protein fragment of SEQ ID NO: 2, including sequences only 6 nucleic acids in length ("...a CLASP-2 protein as shown in SEQ ID NO: 2" [emphasis added]).

Pianese et al. teach an isolated polynucleotide that encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2 of the instant application (See sequence alignment attached to this Office Action as Appendix A; see nucleotides 365-700 of Pianese et al.; see also amino acids 864-975 of SEQ ID NO: 2 of the instant application). Pianese et al. also teach a polynucleotide that has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1 of the instant application (See sequence alignment attached to this Office Action as Appendix B; see nucleotides 230-270 of Pianese et al.; see nucleotides 2466-2496 of SEQ ID NO: 1 of the instant application, for example).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 8-12 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pianese et al. (Genbank Accession No. X68101; 24 February 1999) as applied to claims 1 and 15 above, and further in view of Jacobs et al. (US Patent No 5,965,397).

The teachings of Pianese et al. are set forth above. Pianese et al. does not teach expression vectors, host cells, or a method of producing a polypeptide.

Jacobs et al. teach a vector comprising the cDNA; an expression vector comprising a polynucleotide in which the nucleotide sequence is operatively linked with a regulatory sequence; a host cell; and a method of producing a polypeptide comprising culturing the host cell (claims 1-5 and column 24, lines 31-65; column 25).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to obtain vectors (with control sequences) containing DNA sequences and transfecting them into host cells as taught by Jacobs et al. by cloning the cDNA from DNA described by Pianese et al. The person of ordinary skill in the art would have been motivated to clone the nucleotide sequences described by Pianese because it would allow for the

expression of the polynucleotide and the subsequent characterization of the polypeptide. There is a reasonable expectation of success because transfecting the expression vector into a host cell for the expression of the polypeptide is routine in the art for expression studies and screening for new polypeptides. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

NCI-CGAP. Accession No. AA484945, EST database, 15 August 1997.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
24 January 2007

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER

Appendix A

SCORE Search Results Details for Application 10663538 and Search Result 20061215_122921_us-10-663-538-1.rge.

Score Home Page | Retrieve Application List | SCORE System Overview | SCORE FAQ | Comments / Suggestions

This page gives you Search Results detail for the Application 10663538 and Search Result 20061215_122921_us-10-663-538-1.rge.

start | next page

Go Back to previous page

GenCore version 5.1.9

OM nucleic - nucleic search, using sw model

Run on: December 18, 2006, 13:01:48 ; Search time 43078 Seconds
(without alignments)
7135.783 Million cell updates/sec

Title: US-10-663-538-1
Perfect score: 4807
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Scoring table: IDENTITY_NUC
Gapop 10.0 , Gapext 1.0

Searched: 6366136 seqs, 31973710525 residues

Total number of hits satisfying chosen parameters: 12732272

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

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2: gb_pat:*
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6: gb_ro:*
7: gb_sts:*
8: gb_sy:*
9: gb_un:*
10: gb_vi:*
11: gb_ov:*
12: gb_htg:*
13: gb_in:*
14: gb_om:*
15: gb_ba:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

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Appendix A (cont.)

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	7	3983.4	82.9	6261	2	AX780171	AX780171 Sequence
	8	3522.6	73.3	6207	2	CS165582	CS165582 Sequence
	9	3440.6	71.6	3899	2	AX058220	AX058220 Sequence
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Appendix A (cont.)

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REFERENCE   1  (bases 1 to 3227)
  AUTHORS   Pianese,L.
  TITLE     Direct Submission
  JOURNAL   Submitted (07-AUG-1992) L. Pianese, Dipartimento di Biologia,
            Patologia Cellulare e Molecolare, Via Pansini, Naples, ITALY
REFERENCE   2  (bases 1 to 3227)
  AUTHORS   Pianese,L., Porcellini,A., Avvedimento,V.E., D'Esposti,F.,
            Peliciello,A., Monticelli,A., Musti,A.M., Tortora,G., Varrone,S.
            and Cocozza,S.
  TITLE     A novel thyroid transcript negatively regulated by tsh
  JOURNAL   Mol. Biol. 13, 75-83 (1994)
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ORIGIN

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1037 IleTyrLysLeuIleIleProIleTyrGluLysArgArgAsp........ 1050
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 964 ATCTATAAACTCATCATCCCCATCTATGAAAAGCGGAGGGACTTTAGAGA 1013

1050 ..................................................  1050

1014 CTACCCACCTGTATGACACCCTGCACCGCCCATACAGCAAAGTGACAGAG 1063

1050 ..................................................  1050

1064 GTCATCACTCGGGCCGCAGGCTCCTGGGACCTACTTCCGGGTGGCCTCTT 1113

1051 .........Phe.PheGluAspGluAspGlyLysGluTyrIleTyrLysG 1064
              ::: ||||||||||||||||||||||||||||||||||||||
1114 CGGACAGGGATTCTTCGAAGATGAAGACGGGAAGGAATACATCTACAAAG 1163

1064 luProLysLeuThrProLeuSerGluIleSerGlnArgLeuLeuLysLeu 1080
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1164 AGCCCAAACTCACGCCTCTGTCAGAGATTTCTCAGAGACTCCTTAAACTT 1213

1081 TyrSerAspLysPheGlySerGluAsnValLysMetIleGlnAspSerGl 1097
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1214 TACTCGGATAAATTCGGTTCTGAAAATGTCAAAATGATACAGGATTCTGG 1263

1097 yLysValAsnProLysAspLeuAspSerLysTyrAlaTyrIleGlnValT 1114
     ||||||||||||||||||||||||||||||||:::||||||||||||||||
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1114 hrHisValIleProPhePheAspGluLysGluLeuGlnGluArgLysThr 1130
     |||||||| ||||||||||||||||||||||||||||||||||||||||
1314 CCCATGTGACCCCGTTCTTTGATGAAAAGGAGTTACAGGAGAGGAAAACA 1363

1131 GluPheGluArgSerHisAsnIleArgArgPheMetPheGluMetProPh 1147
     |||||||||||| ||||||||||||||||||||||||||||||||||||
1364 GAGTTTGAACGATGTCACAACATCCGGCGCTTCATGTTCGAGATGCCCTT 1413

1147 eThrGlnThrGlyLysArgGlnGlyGlyValGluGluGlnCysLysArgA 1164
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1414 CACCCAGACTGGGAAGAGGCAGGGTGGCGTGGAGGAGCAGTGTAAGCGAC 1463

1164 rgThrIleLeuThrAlaIleHisCysPheProTyrValLysLysArgIle 1180
     ||||||||||||||||||||||||||||||||||||||||||||||||||
     GGACCATCCTGACAGCAATACACTGCTTCCCCTATGTAAAGAAGCGGATC 1513

     oValMetTyrGlnHisHisThrAspLeuAsnProIleGluValAlaIl 1197
```

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     ||||||||||||||||||||||||||||||||||||||||||||||||||
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1197 eAspGluMetSerLysLysValAlaGluLeuArgGlnLeuCysSerSerA 1214
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1214 laGluValAspMetIleLysLeuGlnLeuLysLeuGlnGlySerValSer 1230
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1231 ValGlnValAsnAlaGlyProLeuAlaTyrAlaArgAlaPheLeuAspAs 1247
     ||||||||||||||||||||||||||||||||||||||||||||||||||
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1247 pThrAsnThrLysArgTyrProAspAsnLysValLysLeuLeuLysGluV 1264
     ||||||||||||||||||||||||||||||||||||||||||||||||||
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1264 alPheArgGlnPheValGluAlaCysGlyGlnAlaLeuAlaValAsnGlu 1280
     ||||||||||||||||||||||||||||||||||||||||||||||||||
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1281 ArgLeuIleLysGluAspGlnLeuGluTyrGlnGluGluMetLysAlaAs 1297
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1814 CGTCTGATTAAAGAGGACCAGCTGGAGTACCAGGAAGAGATGAAAGCCAA 1863

1297 nTyrArgGluMetAlaLysGluLeuSerGluIleMetHisGluGlnIleC 1314
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1864 CTACAGGGAGATCCGGAAGGAGCTCTCCGACATCATCGTGCCGAGAATTT 1913

1314 ysProLeuGluGluLysThrSerValLeuProAsnSerLeuHisIlePhe 1330
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1914 GCCCTG.....GAGAGGACAAGCGTGCTACCAAATTCCCTGCACATCTTC 1958

1331 AsnAlaIleSerGlyThrProThrSerThrMetValHisGlyMetThrSe 1347
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1959 AACGCCATCAGCGGGACACCAACAAGCACAGTGGTTCAAGGGTTGACCAG 2008

1347 rSerSerSerValVal 1352
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2009 TTCATCCTCAGTTGTG 2024

     ... gb pr:AK056684
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Appendix B

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RNTRG
LOCUS       RNTRG                   3227 bp    mRNA    linear   ROD 24-FEB-1999
DEFINITION  R.norvegicus trg mRNA.
ACCESSION   X68101
VERSION     X68101.1  GI:550419
KEYWORDS    trg gene.
SOURCE      Norway rat.
  ORGANISM  Rattus norvegicus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae;
            Rattus.
REFERENCE   1  (bases 1 to 3227)
  AUTHORS   Pianese,L.
  TITLE     Direct Submission
  JOURNAL   Submitted (07-AUG-1992) L. Pianese, Dipartimento di Biologia,
            Patologia Cellulare e Molecolare, Via Pansini, Naples, ITALY
REFERENCE   2  (bases 1 to 3227)
  AUTHORS   Pianese,L., Porcellini,A., Avvedimento,V.E., D'Esposti,P.,
            Feliciello,A., Monticelli,A., Musti,A.M., Tortora,G., Varrone,S.
            and Cocozza,S.
  TITLE     A novel thyroid transcript negatively regulated by tsh
  JOURNAL   Mol. Biol. 13, 75-83 (1994)
FEATURES             Location/Qualifiers
     source          1. .3227
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                     /strain="Fischer"
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                     /cell_line="FRTL-"
                     /clone_lib="lambdaGT"
     gene            1. .2218
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                     /db_xref="SPTREMBL:Q63603"
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                     LQVIISLSQLIADVVGIGGTRFQQSLSIINNCANSDRLIKHTSFSSDVKDLTKRIRTV
                     LMATAQMKEHENDPEMLVDLQYSLAKSYASTPELRKTWLDSMARIHVKNGDLSEAAMC
                     YVHVTALVAEYLTRKEADLALQREPPVFPYSHTSCQRKSRGGMFRQGCTAFRVITPNI
                     DEEASMMEDVGMQDVHFNEDVLMELLEQCADGLWKAERLRAGLLTSINSSSPSMKSGG
                     TLETTHLYDTLHRPYSKVTEVITRAAGSWDLLPGGLFGQGFFEDEDGKEYIYKEPKLT
                     PLSEISQRLLKLYSDKFGSENVKMIQDSGKVNPKDLDSKFAYIQVTHVTPPFDEKELQ
                     ERKTEFERCHNIRRFMFEMPPTQTGKRQGGVEEQCKRRTILTAIHCPPYVKKRIPVMY
                     QHHTDLNPIEVAIDEMSKKVAELHQLCSSAEVDMIKLQLKLQGSVSVQVNAGPLAYAR
                     AFLDDTNTKRYPDNKVKLLKEVFRQFVEACGQALAVNERLIKEDQLEYQEEMKANYRE
                     IRKELSDIIVPRICPGEDKRATKFPAHLQRHQRDTNKHSGSRVDQFILSCVTLPHEPH
                     VGTCFVMCKLRTTFRANHWFCQAQEEAMGNGREKEPWTVIPNSRFYRSWGKVHIFF"
BASE COUNT      905 a    738 c    777 g    807 t
ORIGIN
```

```
  Query Match          28.1%;  Score 1349.8;  DB 10;  Length 3227;
  Best Local Similarity   78.4%;  Pred. No. 0;
  Matches 1838;  Conservative    0;  Mismatches  297;  Indels  210;  Gaps   10;

Qy    2237 catggacataatcctctcatgaaaaaagtttttgatgtctacctgtgtttttcttcaaaaa 2296
           |||||||| ||| |||||||| ||||||||||||||||||||||||||||||| || |||||
Db      11 CGTGGACATAGTCCACTCATGAAGAAAGTTTTTGATGTCTACCTGTGTTTCCTCCAAAAG 70

Qy    2297 catcagtctgaaacggctttaaaaaatgtcttcactgccttaaggtccttaatttataag 2356
           |||||||| |||| ||||||||||||||||||||||||||||||||||| ||||||||||||
Db      71 CATCAGTCAGAAATGGCTTTAAAAAATGTCTTCACTGCCTTAAGGTCATTAATTTATAAG 130

Qy    2357 tttccctcaacattctatgaagggagagcggacatgtgtgcggctctgtgttacgagatt 2416
           || |||||||| ||||| || ||| | || |||||||| || ||||||| || ||| ||
Db     131 TTCCCCTCAACGTTCTACGAGGGGCGGGCAGACATGTGCGCATCTCTGTGCTATGAGGTT 190

Qy    2417 ctcaagtgctgtaactccaagctgagctccatcaggacggaggcctcccagctgctctac 2476
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Qy    2477 ttcctgatgaggaacaactttgattacactggaaagaagtcctttgtccggacacatttg 2536
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Qy    2537 caagtcatcatatctgtcagccagctgatagcagacgttgttggcattggggaaaccaga 2596
           || |||||||| ||| |||||||||||||| |||||||| |||||||||| | |||||||
Db     311 CAGGTCATCATCTCTCTCAGCCAGCTGATCGCAGACGTGGTTGGCATTGGAGGAACCAGA 370

Qy    2597 ttccagcagtccctgtccatcatcaacaactgtgccaacagtgaccggcttattaagcac 2656
           |||||||||||| |||| |||||||||||||||||||||||| || |||||||| ||||||
Db     371 TTCCAGCAGTCCTTGTCTATCATCAACAACTGTGCCAATAGCGACCGGCTCATTAAGCAC 430

Qy    2657 accagcttctcctctgatgtgaaggacttaaccaaaaggatacgcacggtgctaatggcc 2716
           |||||||||||||||||||||||||| || ||||| |||||| || || ||||||
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Qy    2717 accgcccagatgaaggagcatgagaacgacccagagatgctggtggacctccagtacagc 2776
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Db     491 ACAGCCCAGATGAAGGAACATGAGAACGACCCAGAGATGCTGGTGGACCTGCAGTACAGC 550

Qy    2777 ctggccaaatcctatgccagcacgcccgagctcaggaagacgtggctcgacagcatggcc 2836
           |||||||| ||||| |||||||| || |||||||||||||| ||||| ||||||||||
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Qy    2837 aggatccatgtcaaaaatggcgatctctcagaggcagcaatgtgctatgtccacgtaaca 2896
           |||||||||| |||||||| ||||||||||||||||||||||||||||||||||||| |||
Db     611 AGGATCCATGTTAAAAATGGGGATCTCTCAGAGGCAGCAATGTGCTATGTCCACGTGACA 670
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Appendix B (cont.)